ART. II.—ACTION OF THE ALKALOIDS OF OPIUM.

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EVERY one knows that when a full dose of opium is taken, that it produces a sleep which is not like our actual sleep, either in its accession, progress, duration or subsequent effect. All physicians are aware that in some people this drug does not produce sleep, but often hallucination, and in some cases vomiting, and rarely tetanoid effects. The composition of this drug, according to the latest researches* is as follows:

1. Morphia discovered by Sertuerner, - 1804
Its derivatives,
Oxymorphia, " " Schuetzenberger, - 1865
Desoxymorphia, " " Wright, - 1871
Apomorphia discovered by Mathiessen and Wright, 1871
Bromomorphide,
Bromotetramorphine, } " " Wright - - - 1872
Chlorotetramorphine,
2. Codeine (Paverine) discovered by Robiquet, - 1832
Its derivatives,
Dicodeine,
Tricodeine,
Tetracodeine,
Desoxycodeine, } " " Wright, - 1872
Bromocodide,
Chlorocodide,
Apocodeine,
3. Narcotine (opium, anarconite trimethylnonarcotine). discovered by Derosne. - - 1873

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* *Jahresbericht ueber die Fortschritte der Pharmacie*, von Wiggers und Huseman, 1872.

Its derivatives,
Bimethylnornarcotine,
Methylnonarcotine,
Nornarcotine, } discovered by Matthiessen and Foster, - - 1868
Tarconine, discovered by Jörgensen, - - 1869
Cotarnine,
Opianic acid, } " " Woehler, - - - 1844
4. Narceine " " Pelletier - - 1833
5. Pseudo-morphine (Phormine), discovered by Pelletier, - - 1835
6. Thebaine (Paramorphia), discovered by Pelletier, 1835
Its derivatives,
Thebenine,
Thebaicine, } discovered by Hesse, - - - 1870
7. Papaverine, " " Merck, - - 1848
Its derivatives,
Nitropapaverine,
Bromopapaverine, } " " Anderson, - 1855
8. Opianine, " " Hinterberger, - 1851
9. Cryptopine, " " Smiles and T. and H. Smith, - - - - - 1864
Its derivative.
Nitrocryptopine " " Hesse, - - 1872
10. Meconidine, " " " - 1870-1871
11. Lanthopine, " " " " "
12. Codamine, " " " " "
13. Laudanine, " " " " "
14. Laudanosine, " " " " "
15. Protopine, " " " " "
16. Hydrocotarnine, " " " "

The above sixteen principal bodies are securely grounded as organic bases.

DOUBTFUL BASES.

1. Porphyroxine (opin) discovered by Merck, 1837, is denied by Hesse as being a separate base.
2. Metamorphine, discovered by Wittstein.
3. Rhoeadine, " " Hesse.
4. Deuteropine, " " " - - 1871

NON-NITROGENOUS NEUTRAL BODY.

5. Meconine, (Opianyl), discovered by Dublanc, 1836

ORGANIC ACIDS.

6. Meconic, discovered by Sertuerner, - - 1805
7. Thebolactic, " " T. and H. Smith.

The per centage[1] in which some of the alkaloids exist is as follows:

Morphia - - -	2–15	per cent.
Narcotine, - -	4–6	" "
Papaverine, - - -	about 1	" "
Codeine, - - -	less than 1	" "
Thebaine - - -	less than 1	" "
Narceine, - - -	.01–.02	" "

Opium[2] *en masse* causes a sleepy nearly narcotic action, quickly disappearing, whilst morphia produces a deep and prolonged sleep. Morphia disturbs the stomach more than opium and its action is more prolonged. Opium is in some cases better borne than morphia; in others the reverse happens. After either opium or morphia there is a period of excitation which in the case of morphia soon passes into sleepiness, whilst after opium this excitement lasts longer. Opium causes a more lasting tingling in the skin than morphia or codeia, and constipates more than morphia, but does not cause as much diaphoresis. Morphia increases the urinary secretion more than opium.

Dr. Eisenmann, of Würzburg, has shown that opium increases the curative properties of all the heroic remedies, and diminishes their toxic. Bernard found that a subcutaneous dose of morphia causes the amount of chloroform for purposes of anæsthesia to be smaller in quantity.

Dr. Da Costa discovered that the after-effects of morphia could be subdued or prevented by bromide of potassium.

Whilst opium in bulk is narcotic, its alkaloids are tetanic as well as soporific, these elements are powerful and in some cases antagonistic.

It is only by the separate study of them that we can elect the effect which we desire. In the study of poisons there are three sources which can be benefited; they are physiology, toxicology and therapeutics. As, for example, the action of atropia to paralyze the pneumogastric, to counteract an overdose of morphia, or to save cases of poisoning by *agaricus muscarius*, a variety of poisonous mushroom. Whilst the poisons of the mineral kingdom, when introduced into the system, unite to form compounds with albuminous bodies of the tissues causing a destruction of their functions; those of the vegetable, neither alter the tissues nor the blood, but seem to act upon the nervous tissue itself, probably by a chemical union with the same.* Brown and Fraser have shown that the chemical coustitution of an alkaloid has a great influence on the action of a drug, as methylstrychnia acts not like strychnia, but like curarine.

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[1] Hermann's *Toxicologie.*

[2] Köhler's *Handbuch.*

All the alkaloids used by me were obtained from Merck's laboratory, Darmstadt, and were administered hypodermically. In studying the action of them, I made use of frogs and man.

As the action on the frog's heart will be studied, I will briefly give a general view of the cardiac nervous apparatus. There are situated in the heart, nerve masses, called ganglia: Remak's in the sinus venosus; Bidder's in the left auriculoventricular septum and Ludwig's in the auricular septum. The excito-motor are comparable to the steam of an engine, the muscles of the heart to the driving-wheels; whilst Ludwig's ganglia are similar to the fly-wheel or governor. The pneumogastrics are united with the inhibitory ganglia, and when atropine, nicotine, conia, or lobelina are administered, these nerves are paralyzed. When muscarine is administered, the heart is stopped in diastole by excitation of the inhibitory ganglia. If now, atropine is administered, the heart will commence to beat again, but if nicotine is given, no such an effect will take place.

The following experiments illustrates this:

Exp. 1. Frog at 5.8 P. M. Heart beating normally. 5.10

**Pharmakolog. Untersuch.* von Dr. M. J. Rossbach I. Band, 1874. III. *und* IV. Heft.

P. M. .001. gr. muscarine injected into the vein,—heart immediately arrested, makes slight contractions when tapped. 5.17 P. M. 1-40th of a drop nicotine by the vein. Up to 5.20 P. M., no contraction followed, when a milligramme of atropine was injected, and it began immediately to feebly beat.

To explain this, Schmiedeberg assumes the arrangement to be as follows:

Muscarine stops the heart by irritating the inhibitory ganglia, whilst nicotine like atropine paralyzes the pneumogastrics; the former paralyzes only the apparatus connecting the trunk of the pneumogastric with the inhibitory ganglia, but atropine paralyzes the inhibitory ganglia.

Although the inhibitory fibres of the pneumogastric are paralyzed by both atropine and nicotine, yet on irritating the trunks of the vagi it is found that there are accelerating fibres which run in them and are not affected, as in the following experiment:

Exp. 2. Frog was given ½ gtt. drop nicotine subcutaneously. 4.25 P. M.; heart beat 28. 4.27, P. M.; heart beat 36, vagus irritated with Dubois's coil at 130 millimetres. 4.37, P. M.; heart beat 24. 4.40 P. M.; heart beat 32, vagus irritated with Dubois's coil at 50 millimetres. 4.45 P. M.; heart beat 24, ligature placed around the pneumogastric and the nerve irritated on the side of ligature farthest from the heart. 4.46, P. M.; heart beat 24.

Hence, it is inferred that in point of fact the inhibitory fibres are not really paralyzed, but seem so because the ganglia by which they express their action are. If conia is given, there is a true paralysis of the inhibitory fibres because there are no accelerating influences exerted on the heart on irritating the vagi. It was shown that a similar alkaloid, lobelina, paralyzes the pneumogastrics. To discover if it paralyzed the inhibitory ganglia or the trunks of the vagi, or the apparatus connecting the inhibitory ganglia with the trunks of the pneumogastrics the following experiments were made:

Exp. 3. Frog at 8.18 A. M., heart beating 48 per minute, when a little chloride of muscarine was subcutaneously injected. 8.21 A. M.; the heart was arrested in diastole. 8.24 A. M., two drops of the acetate of lobelina were introduced subcutaneously.

8.51 A. M., the heart remains quiet.
8.52 A. M., .001 gramme of atropine under the skin.
8.53 A. M., a feeble contraction is seen.
8.59 A. M., eight contractions.
9 A. M., .001 gramme atropine.
9.5 A. M., eight contractions stronger.
9.10 A. M., " " "
9.12 A. M., twenty "
9.15 A. M., thirty-two contractions.
9.20 A. M., thirty-four "
9.22 A. M., forty "

As will be seen by an examination of the above experiment, sufficient time was given for the lobelina to paralyze the inhibitory ganglia, for it acts slowly, yet it was unable to start the heart as atropine did subsequently. When lobelina was first administered and then muscarine given, the slowing of the heart still took place.

Exp. 4. Frog at 9.32, received two gtt. of lobelina under the skin.

11 A. M., heart beat 52., two milligrammes of muscarine was then injected subcutaneously.

11.4 A. M., heart beat, 48.
11.5 " " " 44.
11.8 " " " 40.
11.14 " " " 32.
11.22 " " " 28.
1.36 P. M. " " 32, .001 atropine.
1.40 " " " 36.
1.42 " " " 40.

Exp. 5. Frog at 1.30 P. M., received three drops of lobelina subcutaneously. 5 P. M., heart beating twenty per minute. A few milligrammes of muscarine was injected by the vein, and the heart stopped in diastole immediately.

These experiments demonstrate that lobelina does not paralyze the inhibitory ganglia like atropine.

Dr. A. B. Meyer* has shown that when the vagi are paralyzed by nicotine, that irritation of the sinus venosus stopped the heart in diastole. Now, if after giving lobelina, irritation of the sinus venosus arrests the heart, there is additional proof that lobelina does not paralyze the inhibitory ganglia.

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*Das Hemmungs-Nervensystem, 1869.

Exp. 6. Frog at 1.21 P. M., received three drops of lobelina. 4 P. M., the sinus venosus was irritated and arrest of the heart in diastole for five seconds followed.

The next question that arises, does lobelina paralyze the accelerating fibres of the pneumogastric, or does it, like nicotine, leave them intact? With this view the next experiment was instituted.

Exp. 7. Frog at 1.20 P. M., had left vagus carefully pre pared and placed on a thread, with one Grove cell eighty-one millimetres high and fifty-eight millimetres in diameter, and Dubois's secondary coil at ninety-three millimetres, the nerve was irritated and the heart stopped in diastole.

1.21 P. M., three gtt. of lobelina given subcutaneously.

1.56 " heart beat 24

1.59 " heart beat 24; vagus irritated at 70 mm. for fifteen seconds.

2.7 P. M., heart beat 26; coil at 70 mm. and pneumogastric irritated.

2.11 P. M., heart beat 24; vagus irritated with coil at 0. Helmholtz's modification of the instrument put on.

2.26 P. M., heart beat 28.

2.27 P. M. heart beat 28, vagus irritated thirty seconds with coil at 0.

2.56 P. M., heart beat 25.

2.57 P. M., heart beat 26, vagus irritated sixty seconds. Coil at 0.

As is seen, there is no increased rapidity of the heart's action such as would take place with nicotine. Now, as lobelina does not act on the inhibitory ganglia, and does paralyze the accelerating as well as the inhibitory fibres of the pneumogastric, the inference is that lobelina paralyzes the vagi by acting on the nerve trunk itself, just as it does on the motor nerves themselves.

The fact that after the administration of atropine, calabar bean is able to slow the heart, has led some to infer that it and muscarine act on different parts, but after atropine is given, Boehm has shown that the heart was slowed some and returned to its original beat on the administration of atropine. I have also seen a similar action take place so that at present there is no very good reason to assume that muscarine and physostigmine act on different ganglia.

CRYPTOPIA.

This body was first discovered by Messrs T. and H. Smith, of Edinburgh, in 1864. It melts at 217° C., is easily soluble in chloroform, scarcely soluble in alcohol and insoluble in ether. It is basic, and forms salts with acids.

Dr. S. W. Mitchell[1] found that one-fifth of a grain of Messrs. Smith's make, introduced under the skin of a pigeon caused death on the third day, which was probably due to other causes, as he supposed.

Dr. Immanuel Munk[2] who obtained the drug from Dr. O. Hesse, of Berlin, arrived at the following conclusions:

1. Cardiac movements were slowed by moderate doses, and through large doses completely arrested; this arrest being due to paralysis of the cardiac muscle.
2. Large doses paralyzed the respiratory centers thus causing death. The spinal centers are also paralyzed and there is a loss of reflex excitability, and disturbance of movement.
3. In warm-blooded animals the cardiac contractions were reduced independently of the lessening of the respiratory frequency. In warm-blooded animals the stoppage of respiration is preceded by violent spasms and convulsions which are not due to asphyxia, for they did not appear when artificial respiration was practiced.

Sippell[3] found that at first it acted as an excitant, then as a paralysant to respiratory centres. That the reduction of the respiratory frequency produces a considerable amount of carbonic acid in the blood which causes convulsions and death. It also reduces the excitability of the spinal cord, motor nerves and muscles. It arrests the heart by paralysis of the cardiac muscle.

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[1] *Amer. Med. Jour.*, Jan., 1870.

[2] *Versuche ueber die Wirkung des Cryptopins.* Thesis, Marburg, 1873.

[3] *Fortschritte der Pharmacognosie, Pharmacie und Toxicologie* von G. Dragendorff, 1874.

Harley* found it to be only one-fourth as powerful as morphia as a hypnotic. It is also a convulsivant, and he states that there are about four ounces of this body to a ton of opium.

The cryptopia was administered in the form of the acetate, it being dissolved with a slight amount of heat.

Experiment 8. Frog at 2:7 P. M., received .02 gramme of cryptopia. 2:30 P. M., there are cramp-like movements, is partially paralyzed and sleeping. 2:39 P. M., posterior extremities only seem hyperæsthetic, the remainder of the body not. A wave of contraction runs from the body outward when it is touched, respiration slower. 2:50 P. M., legs extended. 4:35 P. M., frog is sleeping and recovering. Next morning is still greatly sensitive, and croaks when touched, a characteristic of many of the opium alkaloids. The sensibility is so great that he is elevated on the tips of his four extremities when touched.

Experiment 9. Frog at 10:40 A. M., received .005 gramme of cryptopia subcutaneously, respirations frequent. Animal sits still, but manifests a slight disposition to jump when touched. 10:42 A. M., pupil dilated. 10:45 A. M., hops about. 10:50 A. M. .005 grains of cryptopia. 10:52 A. M., shows little inclination to move, respirations frequent. 11 A. M., 005 gramme injected, is sleeping, fore extremities weak, posterior extremities strong. 11:12 A. M., on irritation the movements are feeble. 11:24 A. M., lies with extremities extended, pupils contracted, respiratory movement now and then. 11:59 A. M., .005 gramme of cryptopia, pulse 11 per quarter of a minute. 12:2 P. M.. 005 gramme of cryptopia. 12:7 P. M., heart beat 4 per quarter, no respiratory movement, occasionally spontaneously struggles. 12:20 P. M., death. Motor nerves irritable with Dubois's coil at 125 millimetres one Grove cell, probe thrust down the spine excites contraction, heart beat four per minute, ventricle in complete diastole, filled with blood, when pricked, beats.

Experiment 10. Frog at 1 P. M., received .015 gramme of cryptopia, at first sits quietly, then leaps away, respiration frequent and pupils dilated. 1.57 P. M., hardly any movement on pinching, no respiratory action. Death at 4 P. M.

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* *St. Thomas Hospital Reports*, 1871, Vol. II., p. 133.

Experiment 11. Frog at 3:37 P. M. received .0025 gramme of cryptopia, some escaping, respirations frequent, pupils dilated. 3:55 P. M. loss of sensibility and motility. 4. P. M. respirations labored, pupil contracted, fore extremities weak. Death at 4:5 P. M.

The action of cryptopia is shown by the above experiments to be as follows: the frog sits still at first, then leaps away, frequency of breathing and dilatation of pupil, loss of coordinating power over the anterior extremities then over posterior, increase and subsequent decrease of sensibility, diminution of respiratory movement, heart slowing and finally diastolic arrest. It is filled with blood.

ACTION ON MOTOR NERVES.

In studying the action on them I employed Dubois' in duction apparatus and a Grove cell. The nearer the secondary coil is approximated to the primary the less is the excitability of the nerve. By tying one of the iliac arteries, I preserved the sciatic nerve of that side from the action of the poison.

Experiment 12. Frog at 11:30 A. M. received .01 gramme of cryptopia subcutaneously, right iliac artery previously ligated. 11.45 A. M. pupils dilated, leaps away with difficulty, respirations slower. 12 M., frog is sleeping, fore extremities weak, respirations slow and superficial. 12:35 P. M., .01 gramme cryptopia, general tremors of the whole body, crawls, movements jerky, unsteady. 12:50 P. M., respirations now and then, pupil contracting, when feet are tapped there are tremulous movements. 1:26 P. M., .005 gramme injected. 1:47 P. M., .005 gramme again injected. 4 P. M., frog dead. No reflex movements upon irritation of central end of sciatic of either side. Motor nerves of poisoned side irritable at twenty-five centimetres, of sound side at 34.5 centimetres. Spine thrust causes movement, heart beat, thirty two per minute.

Experiment 13. Frog at 10:55 A. M., received .025 gramme of cryptopia subcutaneously, some escaping right iliac artery previously tied. 11 A. M., no respiratory movement visible, gasps with mouth opened widely, pupil contracted, hops about, fore extremities weak. 11:7 A. M., sleeping. 11:45 A. M., lies sprawling. 12:30 P. M., dead. Right sciatic irritable at fifty-two centimetres: poisoned sciatic at forty-two centimetres, irritation of spinal cord produces slight twitches in both extremities, heart making a few feeble movements.

These experiments show that it requires a stronger electric current to excite the sciatics which were acted upon by the cryptopia than those which did not receive it. The conclusion necessarily follows that crytopia slightly lowers the irritability of the motor nerves.

SENSORY NERVES.

To study the action on the sensory nerves I ligated the iliac artery on one side which would prevent the poison destroying the sensory nerves in that extremity, though the motor nerves are depressed in their irritability they are yet able to carry nervous impulses, as was shown when the spine was irritated. Hence any want of reflex action must be either in the spinal cord or the sensory nerves.

Experiment 14. Frog received at 11:45 P. M., .03 gramme of cryptopia, right iliac artery previously ligated. 12 M., pupil, after a short stage of dilatation, contracted, respirations now and then. 12.15 P. M., makes slight movements, lies sprawling, pupils contracted, no respiratory movement. 1:40 P. M., dead, no movement on irritating the skin of either posterior extremity. Sciatic nerves ligatured, but no reflex action by irritating their central extremity. Heart does not beat.

Experiment 15. Frog at 12:15 P. M., received .04 gramme of cryptopia. Right iliac artery previously ligated. 12:19 P. M., pupil slightly contracted, makes a respiratory movement now and then, fore extremities weak. On pinching skin of either side no reflex action. 1 P. M., death. Trunk of right sciatic irritated and no reflex movement. These experiments prove that the sensory nerves are probably not at fault, as in the right sciatic they did not receive any poison, and consequently could call out reflex movements if the spinal cord and motor nerves and muscles were able to act. I have previously shown that the motor nerves and muscles were able to carry impulses, so the inference is that the want of reflex action is situated in the spinal cord. The study of a poison on the sensory nerves is difficult and all results on them are not as satisfactory as they might be.

REFLEX ACTION.

For considerable time it has been known that after amputation of the head, the reflex excitability of the spinal cord was increased.

Setschenow discovered that mainly in the thalami optici and corpora striata are situated nerve centres which inhibit reflex action. Now if the thalami optici or the corpora quadrigemina are irritated there is a considerable depression of spinal excitability. To estimate the amount of this reduction a frog is hung up in a vertical direction, and one of his hind feet is allowed to rest in a very dilute solution of sulphuric acid till it is withdrawn. The time that the foot is in the water expresses the amount of inhibition of reflex action, and is measured either by a metronome or clock beating seconds. The cerebrum is ablated to prevent voluntary movements. In the living frog this is done by cutting in a line with the anterior edge of the membrana tympani.

Experiment 16. Frog cerebrum ablated.

Time of reflex movement by thevery dilute acid solution	Seconds.	Heart beat per minute
2.10 P. M.	20.	60
2.14 “	.004 gr. cryptopia	
2.17 “	18	60
2.21 “	18	58
2.32 “	11	48
2.35 “	7	49
2.47 “	7	40
2.54 “	10	36
3 “	no reaction	36

Experiment 17. Frog cerebrum ablated.

12.12 P. M.	10	48
12.14 “	Cryptopia .002 gr.	
12.20 “	6	
12.24 “	9	
12.36 “	5	
12.40 “	6	
12.43 “	9	
12.46 “	12	
12.56 “	15	

1	"	21	
1.6	"	25	
1.7	"	medulla divided	
1.14	"	5	
1.19	"	9	
1.22	"	8	
1.33	"	6	40

These experiments show that cryptopia at first increases and then decreases reflex excitability. Setschenow's centres are not paralyzed, as after their removal the normal increase of reflex excitability takes place. The question that arises here is, is this effect a direct action of cryptopia on the nervous system or is it indirect by the slowing of the heart, or through the hemorrhage of the operation?

The effect on the spinal cord itself will decide on what part cryptopia acts.

Experiment 18. Frog, medulla severed.

		Seconds.	Heart Beat.
2:10	P.M.,	10	
2:11	"	.004 gr. cryptopia.	
2:14	"	9	
2:16	"	10	
2:19	"	9	
2:22	"	7	
2:25	"	6	
2:34	"	12	
2:54	"	14	
3:10	"	19	40

Here cryptopia increases, and then decreases reflex excitability, so that the action of this drug is wholly on the spinal cord itself, and not on the nerve centres of Setschenow.

Now, Weil* has shown that hemorrhage excites the inhibitory activity of Setschenow's centres, but has no action on the reflex activity of the spinal cord, where cryptopia acts. He also has shown that arrest of the heart throws this inhibitory centre into activity, but has no influence that is immediate on the spinal cord.

**Reichert's Archiv.* 1871. No. 3.

Now as the increase and decrease of reflex excitability is wholly spinal, this must be a direct action of cryptopia, and not through slowing of the heart, or hemorrhage from the operative procedures.

ACTION ON THE MUSCLE.

In studying the action on muscle I poisoned the frog with cryptopia, and after a few hours severed the medulla, destroyed the spinal cord, and placed the animal on Marey's myographic table, and attached the tendo-achillis to the myograph of Marey; the nerve or muscle then was irritated and the curve registered. I used as registering apparatus Secretan's second axis. This curve was compared with that obtained from an unpoisoned frog. I found that the height of the muscle curve was less than normal in the cryptopia series.

CIRCULATION.

			Heart Beat.
Experiment 19. Frog at	9:53 A.M.		48
	9:56 "	cryptopia	.01 gr.
	9:57		44
	10:00		40
	10:02		40
	10:36		36
	10:37,	cryptopia,	.01 gr.
	10:49		32
	10:51,	cryptopia,	.02 gr.
	11:18		28
	11:25		26
	12:00 M.		24
	12:30 P.M.,	cryptopia,	.01 gr.
	1:19		20
	2:07		20
	5:00,	beating now and then, heart in diastole.	

This experiment demonstrates that cryptopia slows the heart. Now this result must be due either to an increased activity of the cardio-inhibitory apparatus, or lessened activity of the excito-motor ganglia, or the cardiac muscle itself.

Experiment 20. Frog, vagi divided.

11:12 A.M.	heart beat, 36
11:15 "	cryptopia, .02 gr
11:17 "	32
11:25 "	32
12:00 M.	8
12:10 P.M.	8
12:30	8

12:35 vermicular movement now and then of the ventricle, ventricle in diastole, as is seen during irritation of the pneumogastric.

12:56 P.M.	Infus. digitalis, 2 cubic centimetres.
12:57 "	16 "
2:00 "	heart stopped.

There is certainly no stimulation here of the central end of the central inhibitory apparatus, for such action is excluded by the section of the vagi.

Experiment 21. Frog received at 3:55 P.M., .002 gr. of atropine, and at 4:05 P.M., .005 gr. of cryptopia; 4:12 P.M., .005 gr. of cryptopia: 4:20 P.M., .01 gramme of cryptopia.

4:40 P.M.	Heart beat, - - - -	48
5:25 "	" " - - - - -	32
6:22 "	- - - - - - - - -	32
11:00 "	Heart in diastole, and at rest.	

Here cryptopia, notwithstanding the paralysis of the peripheral end of the cardio-inhibitory apparatus, still arrests the heart. Now this slowing must be seated either in the excito-motor ganglia or in the cardiac muscle itself. As the striated muscles have diminished irritability, and the cardiac muscle soon loses its excitability, it is probable that the slowing is due to weakness of cardiac muscle. The revival of the heart beat by infus. digitalis is also confirmatory evidence, as this drug is a stimulant to cardiac muscle.

ACTION ON MAN.

Experiment 22. Pulse 76; respiration 16 at 6:55 P.M.

6:56 P.M. Cryptopia, gr. ½ by the mouth.

7:20 P.M. Pulse 82; respiration 20; pupil slightly dilated;

slight tingling of the skin; feel sleepy during the evening; there is no nausea.

In accordance with previous observers, cryptopia is a pleasant hypnotic.

THEBAIN.

This alkaloid was discovered by Pelletier and Thiboumery in 1832. Magendie first announced that it was a tetanic agent. Orfila confirmed it, as did also Bernard, Baxt. Mueller,[1] Crum-Brown and Frazer, S. W. Mitchell,[2] Rabuteau and Ozanam.[3] I[4] have also studied it, and found it to be a spinal convulsivant, acting neither on the motor nor sensory nerves or muscles; that it increases the pulse and blood-pressure by an action on the vaso-motor centre and the heart itself, and that the reflex action of the depressor nerve is not interfered with.

Experiment 23. Small frog at 8.27 A.M. received .005 gr. of thebain; 8.29 A.M., pupil dilated, respirations slow; 8.30 A.M., tetanus, pupil contracted; 8.47 A.M., .0025 gr. of thebain; 9.15 A.M., pupil contracted; 10.00 A.M., animal dead; motor nerves are irritable.

As is seen, thebain is a tetanizing agent.

Experiment 24. Frog received .005 gr. of thebain by the stomach at 10.10 A.M; 10.15 A.M., tetanus followed; head severed, but tetanus still occurs occasionally.

As is the case with strychnia, thebain excites convulsions, which are spinal in origin.

MOTOR NERVES.

Experiment 25. Frog, right iliac artery and vein ligated; at 10.18 A.M., when he also received .015 gr. of thebain; 10.22 A.M., tetanus; 10.23 A.M., .005 gr. of thebain; pupil contracted; 11.05 A M., dead; sound nerve responds at fifty centimetres; poisoned nerve at forty-five; spine thrust; causes a few twitches in femoral muscles.

The motor nerves, as well as muscles, retain their normal irritability.

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[1] *Das Thebain, eine Monographie.* Marburg, 1868.

[2] *American Medical Journal,* January, 1870.

[3] Dr. G. B. Woods' *Therapeutics.*

[4] The physiological action of thebain. *Boston Med. & Surg. Jour.* Apr. 1875.

SENSORY NERVES.

Experiment 26. Frog at 10.42 A.M., received .002 gr. of thebain; right iliac artery tied; tetanus follows; death at 11.40 A.M. On irritating the skin of either side, or the central end of the sciatics, there ensues no reflex action.

Experiment 27. Frog, abdominal aorta ligated; .0025 gramme of thebain injected under the skin of the lower jaw; tetanus followed over the whole body.

Experiment 28. Frog at 9.49 A. M. had spinal cord cut below the origin of the nerves of the anterior extremities, the spinal branches of the aorta severed; .0025 gr. of thebain injected under the skin of the lower jaw; 10.00 A.M., convulsions of the anterior extremities, reflex action in posterior extremities; 10.15 A.M., convulsions of anterior extremities, none in posterior extremities, although reflex action still continues.

By the ingenious methods of Brown-Sèquard[1] in experiments twenty-seven and twenty-eight, I found in the first that tetanus supervenes in the posterior extremities when they do not receive any poison; and in the second experiment, that when the spine did not receive the poison, but the sensory nerves of the posterior extremities, there was no tetanus in them. Hence the conclusion is that the tetanus is generated by a direct action on the spinal cord.

ACTION ON THE MUSCLE.

By studying the muscle-curves obtained by the method already detailed under the head of "Cryptopia," I found no change in them.

ACTION ON THE CIRCULATION.

I have shown that in warm-blooded animals the increase of pulse is due to an action on the heart, and the increase of blood-pressure to an action on the vaso-motor centre.

CODEIA.

It was thought by Kunkel[2] to be a narcotic, and that it was distinguishable from morphia by not causing, like the latter, the hyenoid posture, and that it was convulsivant.

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[1] *These pour le Doctoral en Medicine*, par F. W. Bonnefin.

[2] Husemann. *Die Pflanzenstoffe.*

He stated that the cardiac and respiratory movements were increased in frequency. Berthè observed that it caused stupor, paralysis of the posterior extremities, weakening of the heart-beat, diminished respiration, sleep, followed by convulsions, and death. He stated that it produced the hyenoid posture, and saw no acceleration of the pulse or respiration. Bernard[1] observed that it caused a sleep not as deep as that of morphia. On frogs, according to Cogswell and Albers, it was a convulsivant, causing hyperæsthesia.

Baxt[2] observed coma, energetic contractions upon external irritation. Wachs saw in a frog a change of carriage, due to want of power over the adductors, a peculiarity I have also seen after narceine and papaverine; loss of movement, stretching cramps, clonic convulsions. Crum-Brown and Frazer, in rabbits, saw convulsions. My specimen dissolved without color in sulphuric acid, which heated to 150° and cooled, give with nitric acid a blood-red color.

Experiment 29. Frog at 11.16 A.M. received .002 gr. cod. sulph., sits still.

11.25 A.M., .008 gr. cod. sulph., sleeping.

12.00 M. Croaks when touched, hyperæsthetic.

1.10 P.M. Hyperæsthesia very great, so much so that touch throws the body into marked contraction.

Next day, 1.36 P.M., same state; .010 gr. codeia sulph. subcutaneously; 2.27 P.M., tetanus of the whole body on touch. On third day, after poisoning, tetanus, crawls with a trembling gait. During the fourth and fifth day it seemed to have recovered from the tetanus, but on the sixth day it again broke out, and death ensued.

Experiment 30. Frog at 10 A.M. received .002 gr. cod. sulph.; at 10:04 A.M., .002 gr. cod. sulph.; 11.45 A.M., tonic cramps— sleeping. On section of cord the cramps continue.

These experiments show that codeia is narcotic and convulsivant.

ACTION ON MUSCLE CURVE.

Following the usual plan already detailed, I obtained curves, which have a longer period of relaxation than takes place in normal muscle. The curve is similar to that produced by veratria.

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[1] *Lecons sur les Anesthetiques.*

[2] *Reichert's Archiv.* 1869.

ACTION ON CIRCULATION.

Experiment 31.	9.20	A.M.	Heart beat, 46
	9.20	"	Cod. sulph. .002 gramme.
	9.22	"	28
	9.23	"	32
	9.24	"	Cod. sulph. .002 gramme.
	9.25	"	30
	9.28	"	28
	9.49	"	26
	10.00	"	24
	11.05	"	24

Experiment 32. Small frog, .002 gr. atropine subcutaneously.

10.25	A.M.	Heart beat, 36
10.26	"	Codeiac sulph. .002 gr.
10.27	"	36
10.28	"	35
10.31	"	35
10.37	"	30
10.59	"	27
11.10	"	24

Experiment 33. Frog. Vagi cut. Heart beat.

5.02	P.M.	28
5.04	"	Cod. sulph. .010 gramme.
5.05	"	24
5.08	"	20
5.16	"	20
5.28	"	20
5.42	"	20
6.19	"	16

As is seen, the fall of heart-beats occurs after the use of atropine, and section of the vagi. Now as the striated muscle ia affected by codeia, the inference is that the cardiac muscle may suffer the same fate.

ACTION ON MAN.

Experiment 34. At 3.20 P.M., pulse 71; respirations 19; 3.27 P.M., ½ gr. cod. sulph.; no change up to 4.07 P.M., when ½ gr. cod. sulph. was taken.

4.20 P.M. Pulse 76; respirations 22; dilatation of the pupil; feel quite sleepy; tingling through the skin.

5.12 P.M. Very sleepy; lie down; supper was taken at 5 P.M.; pulse 88; respirations 20; pupil dilated.

6.12 P.M. Pulse 80; respirations 20; pupil contracted; recovered fully by 10 P.M., although nausea and depressant action follows.

In my case codeia was a hypnotic, followed by considerable gastric disturbance.

CHLOROCODIDE.

That the paper may be more complete, I shall add to it the existing knowledge of the derivatives of the alkaloids.

Dr. Gee[1] noticed that in a cat it produced salivation; dilatation of the pupils, with restlessness, tetanus and death.

It is extremely bitter, but does not produce in man the aching fullness of quinine.

APOCODEIA.

Dr. Wickham Legg[2] states that the chloride in grain doses in dogs produces in five to ten minutes vomiting, and four to five grains, coma and death.

Its action on man is not anything at all, or feeble.

NARCEIN.

Bernard first stated that this body was an excellent narcotic. This has been refuted by Harley, Dr. S. W. Mitchell, and Dr. Da Costa. Baxt observed that in frogs it produced excitement, and then a half comatose state, without any important alteration of the breathing or heart-beat. There was also depression of irritability. It is quite evident that all the bodies used under the name of narcein, were either impure or totally different articles.

This body dissolved in hydrochloric acid and water without color, with nitric acid, it gave an orange color, with sulphuric acid a yellow color passing into a greenish yellow, and finally a reddish brown.

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[1] St. Bartholomew's Hospital Reports. 1869. *American Med. Journal.* 1870.

[2] St. Bartholomew's Reports. 1870; pp. 97.

Experiment 35. Frog at 2 P.M. received .02 gr. of narcein dissolved in glycerine by heat, and a drop of sulphuric acid.

2.10 P.M. Pupils dilated; respirations more frequent.

2.15 P.M. Violent extension and contraction of posterior extremities; anterior extremities normal, whilst legs are extended they are in a series of vibratory movement.

2.51 P.M. .02 gr. narcein.

4.49 P.M. Same state; .08 gr. narcein given.

5.00 P.M. Anterior and posterior extremities in a tetanic state; frog sleeping.

5.20 P.M. Death; motor nerves irritable, also muscles; spine on thrust feebly irritable; heart stopped in diastole, not irritable on pricking.

This experiment demonstrates narcein to be narcotic and convulsivant.

Experiment 36. Frog; left iliac artery ligated; received .011 gr. narcein subcutaneously at 8.30 A.M; 8.45 A.M., stiffness of movement in posterior extremities; as Wachs observed with codeia, I saw difficulty in adducting the legs; no trouble with anterior extremities.

10.00 A.M. Convulsions of a tetanic character in both posterior extremities.

11.45 A.M. Recovered.

As has been first shown, the cause of the convulsive movement is not situated wholly in the muscles, as it takes place in the ligated extremity, and consequently has not its seat in irritation of the endings of the sensory nerves, or endings of motor nerves; necessarily part at least of these convulsive movements must be spinal in origin.

Now, if curare is given, the endings of the motor nerves are paralyzed, and any convulsive movement will be due irritation of the muscle itself.

Experiment 37. Frog at 8.47 A. M. received .011 gramme of narcein, tetanic convulsions in posterior extremities followed.

9.16 A. M. Leg amputated, and still spontaneous contractions in the severed leg.

12 M., curare given.

1 P. M., contraction still observed in muscle of the body on irritation.

Experiment 38. Frog at 9.40 A. M. curarized. 9.48 A. M., completely paralyzed; narcein, .055 gramme given. 10.48 A. M., .011 gr. narcein.

11.24 A. M., on tapping, femoral muscles contract and twitchings ensue.

2.40 P. M. These twitchings still continue, although frog is perfectly motionless.

As is seen, part of the convulsive movements of narcein are muscular, for they supervene after use of curare in large doses, which has the property to destroy the motor nerves, as has been proved by Drs. S. W. Mitchell and Hammond. Hence narceine is narcotic, and produces convulsions by spinal and muscular irritation.

ACTION ON THE MUSCLE-CURVE.

On studying the action on the curve of a muscle, it was seen that narcein produced a veratroid contraction of striated muscles.

ACTION ON THE CIRCULATION.

Experiment 39. Frog at

8.40 A. M.,	heart-beat 46.
8.47 "	narcein .011 gr.
8.48 "	28.
8.51 "	32.
9.00 "	32.
9.12 "	36.
9.16 "	spontaneous convulsion
9.46 "	24.
9.48 "	24.
11.24 "	20.

Experiment 40. Frog; vagi severed.

	Heart-beat.
12.34 P. M.	44.
12.35 "	narcein .011 gramme.
12.37 "	40.
12.47 "	36.
1.03 "	28.
2.40 "	24.

During the afternoon heart stopped, irritable on pricking.

Experiment 41. Frog; vagi cut.

		Heart-beat.
3.36 P. M.		36.
3.37 "	narcein	.011 gr.
3.38 "		32.
3.40 "		32.
3.44 "		32.
3.50 "		30 arrest in diastole for a few seconds.
3.52 "		16.

Experiment 42. Frog. Atropine, .002 gr.

12.00 M.		48.
12.04 P. M.	narcein	.055 gr.
12.07 "		44.
12.11 "	narcein	.055 gr.
12.12 "		48.
12.15 "		48.
12.35 "		48.
12.49 "		42.
1.04 "		42.
2.40 "		38.

As is seen, narceine reduces the heart-beat after the section of the pneumogastrics, but after the preliminary use of atropine, the heart regains its original number of beats and remains there some time, so that there is a stimulation of the peripheral end of the pneumogastric.

ACTION ON MAN.

Experiment 43. 3.25 P. M., heart-beat 64, respiration 20.

3.26 P. M., narceine sulph. ½ gr. by the mouth.

3.54 P. M., pulse 72, respiration 20, pupil same size.

4.00 P. M., sense of constriction through the temple. No hypnotic action observed.

Experiment 44. 10.54 A. M., pulse 64, respiration 20.

10.55 A. M., narceine sulph. gr. 1., which immediately produced a constriction about the temples.

11.30 A. M., pulse 64.

2.20 P. M. No hypnotic action during the day, but headache present.

Like Drs. Mitchell and DaCosta, I never found narceine to have the slightest hypnotic effect. It is, however, a splendid article to produce headache. The only narcotic effects observed were seen in cold-blooded animals.

PAPAVERINE.

Bernard and others think it to be a convulsivant, whilst Baxt thought it to possess hypnotic qualities, and that it reduces the heart-beat by stimulating the cardio-inhibitory apparatus. He states that it reduces the irritability by paralysis of the reflex activity.

Leidesdorf thought it to be a hypnotic in man.

PAPAVERINE.

Nitric acid colored the crystals blue.

Experiment 45. Frog at 3.20 P. M. received .02 gramme dissolved in water with a drop of hydrochloric acid.

4 P. M. Tetanus in the posterior extremities of spontaneous origin; is in a semi-comatose state.

Experiment 46. Frog at 3.16 P. M. received .02 gramme dissolved in glycerine with a drop of sulphuric acid. 3.22 P. M., hops about. 4 P. M., tetanus of posterior extremities. 5 P. M., recovering, is in a semi-comatose state.

Experiment 47. Frog poisoned with curare. When motionless, .02 gramme of papaverine given, dissolved by sulphuric acid. No muscular twitchings were seen, but on placing the muscle in connection with the myograph, the curves were veratroid.*

Experiment 48. Frog received .02 gramme papaverine. Convulsions followed. The medulla was severed and they still continued. When the leg was amputated it had twitchings.

As is seen, papaverine produces a semi-comatose state, and is a convulsivant. As the twitchings continue in the amputated leg, it is evident that the convulsions are partly by an action on either the motor-nerve ends or the muscles, quite probably the latter. It also produces a disturbance in the innervation of the adductors of the lower extremities as does codeia.

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* Ott. *Action of Medicines.*

ACTION ON THE MUSCLE-CURVE.

The striated muscle-curve is veratroid.

CIRCULATION.

Experiment 49. Frog; at

11.13	A. M., heart-beat	32.
11.15	"	.01 gr. papaverine.
11.18	"	24.
11.19	"diastolic arrest	16.
11.21	"	32.
11.54	"	32.
12.12	P. M.	.01 gramme.
12.14	"	diastolic arrest.
12.15	"	24.
12.23	"	32.
2.13	"	20.

Heart makes now and then very feeble movements; motor nerves irritable; spine feebly so; infusions of digitalis cause heart to pulsate per minute twenty-four pretty strong beats, which soon disappear.

Experiment 50. Frog at

11.45	A. M. received	.002 gr. atropine
11.50	"	44.
11.52	"	papaverine .01.
11.53	"	40.
11.54	"	40.
11.56	"	44.
12.08	P. M.	.01 gramme papaverine
12.09	"	36.
12.12	"	36.
3.22	"	36.

After the use of atropine, papaverine has little effect on the heart, which causes the inference that it reduces the heart-beat by peripheral stimulation of the cardio-inhibitory apparatus.

ACTION ON MAN.

Experiment 51. At 2.4 P. M., pulse 68; 1 grain of papaverine taken.

3.27 P. M. Pulse 68; 1 grain of papaverine taken,

4 P. M. Feel quite sleepy, lie down; pulse 68.

5 P. M. Have some pain and tension about the forehead; not so much sleepiness; recovering; no nausea.

I agree with Leidesdorf that this substance is hypnotic.

NARCOTINE.

It is by some thought to be narcotic, by others to be worthless as such. Bernard thinks it to be convulsivant, in which statement Baxt concurs, as well as Dr. S. W. Mitchell. Baxt states that in frogs it produces a half-comatose state.

When I treated it with concentrated sulphuric acid the solution became yellow, and finally a reddish yellow. By heating the solution it became yellowish-red, then bluish-violet on the edge, and finally a reddish-violet.

NARCOTINE.

Experiment 52. Frog at 11.28 A. M., received .002 gr. of narcotine sulph. 11.45 A. M., spontaneous convulsions. 12.10, medulla severed, but twitchings and tetanus still continue.

Experiment 53. Frog received .01 gramme of narcotine sulph. at 1.42 P. M. 7.40 P. M., there are convulsions, which continue after the severance of the medulla; there are no twitchings in the amputated leg.

Experiment 54. Frog at 11.49 A. M. received .020 gr. of narcotine dissolved in water by the aid of sulphuric acid.

3 P. M. Hyperæsthesia; received .020 gr. of narcotine sulph.

3.12 P. M. High state of hyperæsthesia; on pinching croaks.

3.24 P. M. Tetanic contractions of posterior extremities.

Next day hyperæsthesia; croaks when touched; hyperæsthesia for some days; recovers fully.

As is seen, narcotine produces hyperæsthesia and convulsions, which are of spinal origin, as they persist after severance of the medulla.

CIRCULATION.

Experiment 55. Frog at 9.49 A. M. Pulse 34.
9.50 " Narcotin. sulph. .002 gr.
9.51 " 20.

9.54 " 14 systole.
quick; diastole slow.
10 " 12.
10.4 " 10.
10.7 " 14.
11.5 " 16.

Experiment 56. Very small frog. Atropine previously given.

10.27 A. M. Heart-beat 28.
10.28 " Narcotin. sulph. .002 gr.
10.30 " 16.
10.30 " 2.
Diastole 15 seconds.
Systole 1 second.
11.10 " 4.
Heart immediately responds to stimulus.

Experiment 57. Frog. Atropine .002 gr.

11.25 A. M. 36.
11.26 " Narcot. sulph. .002 gr.
11.27 " 36.
11.29 " 28.
11.31 " 24.
11.32 " 16.
11.38 " 12.
11.45 " 8.

Experiment 58. Frog. Nicotine 1-20 gt.

11.50 " 40.
11.56 " Narcotin. sulph. .002 gr.
11.57 " 40.
12 M. " 28.
12.3 P. M. 24.
12.16 " 20.
12.30 " 14.

Experiment 59. Frog. Heart-beat. Vagi cut.

5.10 P. M. 44.
5.14 " Narcot. sulph. .020 gr.
5.15 " 40.
5.24 " 16.

5.30 "	12.
5.38 "	14.
5.42 "	12.
7.32 "	8.

These experiments demonstrate that narcotine has what has hitherto escaped notice—a very marked effect on the heart of cold-blooded animals. No other alkaloid of opium, that I am aware of, is its equal in the same dose, as regards cardiac effect. This slowing of the heart is not due to stimulation of the cardio-inhibitory apparatus, but is produced by an action on the muscle, as the systole in one experiment occupied only one second, whilst the diastole occupied fifteen. Now, narcotine affects striated muscles in a similar manner, for then contraction (systole) is quick, but relaxation (diastole) is slow, as is shown in the muscle-curve.

Experiment 60. Action on man.

At 2 P. M. one grain of narcotine sulph. taken. No narcotic effect observable.

4 P. M. Another grain taken, which also produced no effect.

COTARNINE.

Bucheim and Loos[1] have shown that in frogs it produces an increasing sleepiness and lassitude, the breathing is superficial, the animal lies on its abdomen, the extremities are not drawn up and are insensible to irritation. Its action is similar to that of curare. It produces, like it, paralysis of the motor nerves. As after curare, it produces in the frog dropsy in a few days.

HYDROCOTARNINE.

Falck[2] states that as a toxic agent it is weaker than codeia or thebain, but more fatal than morphia. The color of the blood is dark. Its action reminds one of codeia, that is, narcotic and convulsivant. The tetanic form begins with an increase of respiratory frequency which can be heard, and is often whistling, excitement, licking of body and salivation, active movement of the ears, whose blood vessels at one time are strongly congested, at other times anemic, gradual or sudden dilatation of the pupil, trembling, spasmodic contractures which go into opisthotonus, with diminished respiration, relaxation and death, when the pupils narrow. In this form of poisoning, the thermometer rises. In the narcotic form, there is increased respiration and, after mydriasis, injection of the ears, restlessness and trembling, with contraction and the head sinks down; intercurrent convulsive movements come on till death. Here the temperature sinks. Frogs go into tetanus under it, but the heart beats thirty-six to forty-eight hours after apparent death. A heart brought to a stop by muscarine is started by hydrocotarnine.

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[1] Eckhard's *Beitraege*, V. Band. 2 Heft.

[2] *Toxikolog.* Studien ueber das Hydrocotarnin,

HYDROCHLORATE OF COTARNAMIC ACID.

This body is produced by the action of hydrochloric acid to cotarnin. Wickham Legg states that in the dog it produces flickering contractions and weakness, the intellect seems perfect; falls over on his side; is insensible to ordinary stimulus; respirations fall with the pulse; spasms of the muscles, lasting ten seconds, and death. In other cases, vomiting and purging ensued before the just mentioned symptoms. The temperature and respirations fell, then rose and again fell. The pulse was greatly increased, but finally fell. It requires a considerable time for it to act, in some cases days. It has little influence on the motor nerves or muscles of mammalia, but frogs soon lose their muscular irritability. The vagus is paralyzed. The slowness of the development of the symptoms was thought to be due to the slowness of absorption.

LAUDANOSINE.

Wortmann* states that in rabbits it excites more and more the centres of respiration. The excitation spreads to the brain and spinal cord in such a violent manner that tetanus ensues, which, producing asphyxia, is the cause of death. The vasomotor centre is paralyzed, or at least considerably reduced in irritability, as there was injection of the ears and increased flow of saliva. The minimum fatal dose is 67.5 millgrammes to one kilogr. of body-weight of rabbit, when administered subcutaneously.

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* *Jahresbericht uber Pharmacognosie*, 1874.

LAUDANINE.

Falck compared it with strychnia and brucia in its action. Its minimum fatal dose is .025–.03 gramme to one kilogr. of body-weight, and of hydrocotarnin .16 gr. to one kilogr., body-weight, so that in toxic power thebaine is first, then laudanin, then hydrocotarnine, then morphia, and then laudanosine. After death by laudanine, the left heart contains dark-red blood. As in thebain, Falck states that there are three periods. It causes an increase of respiratory frequency, due to an action on the respiratory centre. Finally there were convulsions and trembling. In the second period of opisthotonus emprosthotonus and trismus, during which no respiration takes place, and the pupil for the most part is dilated. Then follows relaxation of the muscles and limbs, adynamia, and death from the brain outward; the heart dies last.

MORPHIA.

Small doses cause acceleration of the heart, and later, sleepiness. Large doses increase the cardiac and respiratory frequency, the skin is warm and flushed, there is a sense of tickling in the skin, and a period of excitement. In the second period the respiratory and cardiac frequency sinks, the heart-beat is weak, and sleep follows. By subcutaneous injection there is a benumbing action at the place of injection. Lichtenfels discovered that when morphia was introduced either by the mouth or subcutaneously, that it diminished the sensibility to taste, which decrease was greater on the injected side. On frogs it acts like strychnia in many respects. On dogs it causes sleep, loss of reflex action except in the cornea. After waking they creep away, have a hyenoid gait. Dr. S. W. Mitchell has shown that pigeons have an especial immunity against it. In small doses* the pulse, as in man, is first accelerated, and then retarded. If it is injected into the veins, slowing takes place first, then acceleration of the heart. This slowing is a result of both central and peripheral stimulation of the vagus, and the acceleration is due to its paralysis. If all the nerves going to the heart are sev-

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*Gscheidlen. *Untersuch, a. d. Physiolog. Lab. in Wuerzburg*, II., 1.

ered, then morphia causes a small acceleration and a considerable slowing. The arterial blood-pressure is elevated then lowered, due to stimulation and subsequent paresis of the vaso-motor centre. In dogs the flow of saliva is increased. According to Nasse[1] it increases intestinal peristalsis. It retards the breathing, and section of the vagi does not prevent it. The motor-sensory nerves and reflex actions are first increased and then decreased. Meihuizen[2] saw morphia depress reflex action, then return it to normal, and finally excitation. According to him, cramps ensue which are not of a reflex nature. The alkaloid is found in the urine, liver, and blood.

MORPHIA.

Experiment 61. Frog at 11.23 A. M. receives .010 gr. of sulphate of morphia. 1.36 P. M., .050 gr. 2.27 P. M., is sleeping.

6 P. M., some hyperæsthesia.

Next day, 12 M., relaxed dozing; when touched is elevated on his extremities and is croaking.

8.35 A. M., on third day, tetanus, which continued to the seventh day, when the animal died.

Experiment 62. Frog at 10.10 A. M., received .1 gr. of sulphate of morphia. 12.30 P. M., sleeping. 2 P. M., skin of back discolored to a dirty yellow, where the solution touched subcutaneously.

Experiment 63. Frog at 10.20 A. M., received .010 gr. of morph. sulph. During the day hyperæsthesia and sleep. Next day, at 10.10 A. M., convulsions, which continued after severing the medulla.

Experiment 64. Frog; at 10.04 A. M., heart-beat 44.

10.07	"	.010 gr. morph. sulph.
10.08	"	40.
10.10	"	40.
10.42	"	40.
3.05	P. M.	36.

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[1] Beitraege zur Physiologie der Darmbewegungen. Leipzig: 1866.

[2] *Pflueger's Archiv.*, VII., 201.

As is seen, morphia is a tetanic agent, the seat of the convulsions being spinal. It also is narcotic. Its action on the heart of cold-blooded animals is very small.

ACTION ON MUSCLE.

It also produces veratroid contraction of the muscle.

OXYMORPHIA.

This is an oxidation product of morphia.

Dr. Kreis, in Hermann's laboratory, found that in frogs and dogs it had an extremely weak action like morphia. He perceived no action when .4 gramme was taken.

APOMORPHIA.

This body is obtained by heating morphia with hydrochloric acid; and was discovered by Matthiessen and Wright. It has no narcotic properties ; it is an emetic. Asphyxia has no influence on its emetic power. It hastens the pulse by an action on the accelerator. Later, like all other emetics, it slows the pulse. There is no change of blood-pressure. The breathing is accelerated during the increased rapidity of the heart's action. It excites and depresses spinal irritability. Muscular irritability is reduced.

Exp. 64 a. Frog at 10.30 A. M. received .010 gr. of apomorphia. During the day there was hyperæsthesia and twitchings ; no vomiting. Like Köhler, I have never seen them vomit ; although, as Drs. Mitchell and Hammond have observed, I have seen a frog put his stomach out of his mouth after a dose by the mouth of veratria. Next morning there was paralysis of voluntary movement; lies with legs extended; croaks hyperæsthetic; touching him brings out convulsions.- After section of the medulla, they continued.

Exp. 65. Frog at 6.28 P. M. received .010 gr. of apomorphia. There followed hyperæsthesia, dragging of posterior extremities, and finally loss of all reflex action. Death at 9.40 P. M.

Apomorphia, as is seen, excites and then depresses spinal irritability ; the muscle curves show that muscular irritability is reduced.

Exp. 66.	Frog.	5.28 P. M.	Heart-beat 32.
		5.29 "	Apomorphia .010 gr.
		5.31 "	36.
		5.32 "	32.
		5.37 "	28.
		5.41 "	28.
		6.19 "	24.

Its action on the heart is a lowering one.

MECONINE.

According to Dr. S. W. Mitchell it simply produces in pigeons an emetic effect. Harley believes it to have a weak hypnotic action which was not observed by Dr. Mitchell.

When my specimen was added to concentrated sulphuric acid it gave a purple color which by addition of water throws down a brown precipitate, which in ammonia solution gave a reddish color, disappearing on agitation.

MECONINE.

Exp. 67. Frog at 1.15 P. M. received .020 gramme of meconine dissolved in glycerine by the aid of heat. Hyperæsthesia followed. 3.10 P. M. .020 gramme meconine in warm water. 5.45 P. M. .010 gramme in hot water, some escaping. 6.32 P. M. extremities relaxed, frog is sleepy. For the three subsequent days there was paralysis of voluntary movement, extremities relaxed and extended. When touched, croaks.

As is seen meconine causes hyperæsthesia and subsequent relaxation, with a little sleepiness.

Exp. 68.	Frog at 1.13 P. M.		Heart 32
	1.15	meconine .050 in hot solution.	
	1.16		32
	1.25		36
	1.34		32
	1.54		26
	2.30		32
	3		32

It has little or no action on the heart in small doses.

ACTION ON MAN.

Exp. 69. At 11.27 A. M., pulse 64, respirations 20.

11.32 A. M., meconine—2 grains in water by the mouth.

1.32 P. M. Pulse 64, respirations 20 during the afternoon. No hypnotic effect.

In accordance with late observers, this article has no soporific effect. The difficulty of dissolving it may be one reason.

The following expresses the conclusions to which I have come in the light of my experiments:

1. Cryptopia is narcotic; excites, and then depresses reflex action by an effect on the spinal cord, reduces power of motor nerves, abolishes sensation by an action on the spinal sensory ganglia, and lowers the heart beat by an action on its muscular structure.
2. Thebaine is a spinal convulsivant, has no action on motor or sensory nerves, or striated muscle. It reduces the heart-beat by an action on that organ, and increases blood-pressure by stimulating the cerebral vaso-motor centre.
3. Codeia is a narcotic and spinal convulsivant; produces a veratroid contraction of striated muscle, and depresses the heart-beat by an action on the cardiac muscle.
4. Chlorocodide is a tetanic agent.
5. Apocodeia produces vomiting, coma and death.
6. Narceine is soporific to cold-blooded animals, but not to man, and is a spinal convulsivant. It does not destroy the motor nerves, as they act on thrusting a probe down the spine. It produces veratroid contraction of the muscle, and reduces the heart-beat by stimulation of the peripheral end of the pneumogastric.
7. Papaverine is narcotic and convulsivant; the convulsions being partly spinal and partly peripheral, the latter it is highly probable, from an action on the muscle. It diminishes the heart's contractions by peripheral action on the cardio-inhibitory apparatus. It also causes veratroid contraction of the muscle.
8. Narcotine is non-narcotic, and a spinal convulsivant; produces veratroid contraction of striated muscle, and is a very active agent to decrease the beats of the heart by an action on cardiac muscle.

9. Cotarnine is soporific, and paralyzes like curare the motor nerves.

10. Hydrocotarnine is narcotic and convulsivant.

11. Hydrochlorate of cotarnamic acid is a convulsivant, and paralyzes the pneumogastric.

12. Laudanosine and laudanine are tetanic agents.

13. Morphia is a narcotic and spinal convulsivant. It produces veratroid contraction of muscle, and reduces the heart-beat.

14. Oxymorphia has an action like morphia, only weaker.

15. Apomorphia is an emetic, excites and reduces spinal reflex excitability, and diminishes the number of cardiac contractions.

16. Meconine is narcotic to cold-blooded animals, but not in doses of two grains by the stomach in man. It causes hyperæsthesia and paralysis of voluntary motion with general relaxation. It also produces a veratroid contraction.

As has been stated, the alkaloids of opium all have a dominant action on the nervous system, causing first increased exaggerated functions, and if the dose is large enough, a paralysis of them. In cold-blooded animals this action is mainly spinal, because all their functions are mainly spinal. But as the spinal functions are subordinated to the action of the cerebral ganglia in the animal kingdom, so there is not so much spinal action, and more excitation and depression of the cerebral actions. Morphia in cold-blooded animals brings out the spinal actions, tetanus, whilst in man it brings out the cerebral actions which usually mask the spinal action, although occasionally there is seen only a spinal action and an excitation of the cerebral action. In such cases the fault is in the nervous constitution of the individual, the spinal functions not being under the control of the cerebral. Other excitants cause in children general convulsions which in the adult are without effect, because the predominance of the spinal functions are subordinated more in the adult to the cerebral ganglia than in childhood. As to the reasons why one element of opium is active in a lower animal and useless in man, the march of experimental science will decide; for the experimental study of the action of drugs is well able to take care of itself, thanks to the labors of Bernard in France, Von Bezold, Böhm, Köhler, Schmiedeberg, Rossbach, and others, in Germany; to Brunton, Crum Brown, and Frazer, in England; Drs. S. W. Mitchell, Amory, and H. C. Wood, Jr., in this country.

I have appended here a table, showing approximately the soporific, convulsivant, and toxic relations of the elements of opium. They are arranged in the order of their strength. Some have been studied so little that their true place in the series cannot at present be definitely laid down.

Narcotic Effect.		Convulsivant Effect.	Toxic Effect.	
MAN.	ANIMALS.	ANIMALS.	MAN.	ANIMALS.
Morphia ...	Morphia....	Thebaine.......	Morphia ...	Thebaine.......
Codeia	Codeia	Laudanine	Codeia	Laudanine .....
Cryptopia ..	Cryptopia...	Laudanosine ...	Cryptopia ..	Laudanosine ...
Papaverine..	Narceine ...	Hydrocotarnine.	Thebaine ...	Hydrocotarnine.
....	Meconine ..	Papaverine	Papaverine .	Morphia ....
....	....	Narcotine	Narceine ...	....
....	....	Codeine	Narcotine ..	....
....	....	Morphine	....	....

ART. III.—THE COST OF CONSTRUCTING HOSPITALS FOR THE INSANE.

BY I. RAY, M. D.

(Read to the Convention of Superintendents of Hospitals for the Insane, held at St. Louis, June, 1877.)

NOTWITHSTANDING our abundant experience in the building of hospitals for the insane, the prevalent notions respecting their cost are pervaded by a degree of vagueness and uncertainty hardly to have been expected from such experience. The fact is calculated to create a very unsatisfactory state of public feeling respecting the present methods of caring for the insane. Once, every State had come to the conclusion, in the fullness of time, that it was bound to provide for their